Are we ready for a randomized trial of valproic acid in newly diagnosed glioblastoma?

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Valproic acid is a well-established antiepileptic drug with a still enigmatic mode of action. The drug acid has been proposed to work by inhibiting various ion channels or promoting GABA signaling, moreover, it also exhibits pharmacodynamic properties likely to be unrelated to its antiepileptic activity, including inhibition of histone deacetylases (HDAC). In contrast to classical enzyme-inducing antiepileptic drugs, valproic acid is a multiple enzyme inhibitor, targeting amongst others UDP-glucuronosyltransferase, epoxide hydroxylase and CYP2C coenzymes.[1]

The first therapeutic applications of valproic acid in neurooncology beyond its role as an antiepileptic drug stem from the pediatric literature where valproic acid was assumed to induce differentiation of tumor cells. In recent years a growing list of retrospective analyses have indicated that glioma patients exposed to valproic acid have a superior outcome,[2-4] including an analysis of patients treated within the registration trial for temozolomide in newly diagnosed glioblastoma.[5]

In the present issue of Neuro-Oncology, De Wit-Kerkhof and colleagues studied the effect of valproic acid on seizure control and survival in patients with glioblastoma diagnosed and treated from July 1999 until September 2011.[6] Of 291 patients, 181 had seizures and were treated with valproic acid or levetiracetam or their combination and had a minimum follow-up of six months; 108 of these patients were treated with temozolomide and valproic acid for at least 3 months. The analysis of efficacy of antiepileptic drug treatment was limited to patients with a minimum follow up of 6 months. For the analysis of survival effects of antiepileptic drug treatment, a minimum duration of 3 months of the combination of temozolomide and valproic acid was

required. Both these aspects of the study design introduce a significant bias that needs to be considered when analysing the data. This is because these measures select for favourable course patients since progression would have led to either discontinuation of temozolomide, or possibly increased seizure activity and a change of the antiepileptic drug regimen, or rapid deterioration incompatible with further follow-up, or combinations thereof.

Freedom from seizures was achieved with monotherapy in 41 of 100 patients treated initially with valproic acid (41%) and in 16 of 37 patients treated initially with levetiracetam (43.3%). Using either drug alone or in combination, 89 of 116 patients (76.7%) became seizure-free overall.

For the survival studies the authors then proceeded to analyse 108 patients treated with valproic acid and temozolomide for at least 3 months. They were compared to 57 patients treated with valproic acid for less than 3 months or another antiepileptic drug or no antiepileptic drug at all. These two groups were reported to be balanced regarding major patient characteristics including O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status. Patients treated with valproic acid had a longer medium survival of 69 weeks (95% CI 61.7-67.3) compared with 61 weeks (95% CI, 52.5-69.5) in those not receiving valproic acid for 3 months (HR 0.63, 95% CI 0.43-0.92) (p=0.016). The difference in progression-free survival between these groups was not significant (p=0.06). Surprisingly, neither extent of resection nor *MGMT* promoter methylation status, but only age and valproic acid treatment were significant prognostic factors on multivariate analysis in this subgroup of 165 patients (Table 3).

While this analysis adds to the literature supporting a disease course-modifying role for valproic acid in glioblastoma, it has several limitations: the patients were collected

over a long time period, *MGMT* promoter methylation data were available for less than half of the patients, and the inclusion criteria for analysis in the subpopulations introduce a bias as outlined above that is difficult to estimate but likely has an impact. This is illustrated by the fact that neither complete resection nor *MGMT* status retained prognostic significance on multivariate analysis in Table 3. Besides small numbers, notably for *MGMT* where approximately half of the patients had no status available, this striking observation is most likely explained by the fact that poor prognosis patients had *a priori* been eliminated from this analysis by its very design. This is corroborated by the data shown in Table 4 which show a rate of total resections in the range of 80%, which is double the rate usually reported, and a relatively higher rate of *MGMT* promoter-methylated patients in the valproic acid group. Interestingly, as in the analysis from the EORTC NCIC-trial,[5] valproic acid given early on in the disease course had no effect on progression-free survival, but only an effect on overall survival. This is difficult to explain on a biological basis unless we assume once more that we are not able to reliably measure progression or that valproic acid pretreatment primes glioblastomas for favourable responses to salvage therapies.

The present study supports the evidence of a survival-promoting effect of valproic acid in glioblastoma. However, all the analyses supporting this view carry inherent limitations: they are all retrospective, there was commonly no in depth study of duration and intensity of exposure to the drug, and the number of patients in each of these series was relatively small. In the absence of promising pharmacological agents in the treatment of newly diagnosed glioblastoma, it is obvious that there is now significant interest in exploring a possible inclusion of valproic acid into the standards of care for newly diagnosed glioblastoma.

This would, however, require a randomized trial which is going to be a rather expensive, large trial if conducted in the US or Europe today, without a commercial sponsor to support such an endeavor. This does not mean that such a trial should not be done if the scientific community believes that it should be done. However, before such a clinical trial concept is moved forward, it seems to be mandatory to make use of contemporary prospective clinical trial populations where comedication has been captured with precision, including RTOG0525, CENTRIC and AVAGlio. A joint analysis of these patient populations exploring the potential impact of comedication with valproic acid should guide us in determining whether the next step, a randomized phase II trial of valproic acid in newly diagnosed glioblastoma, should be undertaken or not.

References

1. Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why, and what to do about it? *Lancet Oncol* 2012;13:e375-e382.

2. Oberndorfer S, Piribauer M, Marosi C, Lahrmann H, Hitzenberger P, Grisold W. P450 enzyme inducing and non-enzyme inducing antiepileptics in glioblastoma patients treated with standard chemotherapy. *J Neurooncol* 2005;72:255-260.

3. Felix FH, Trompieri NM, de Araujo OL, da Trindade KM, Fontenele JB. Potential role for valproate in the treatment of high--risk brain tumors of childhood-results from a retrospective observational cohort study. *Pediatr Hematol Oncol* 2011;28:556-570.

4. Barker CA, Bishop AJ, Chang M, Beal K, Chan TA. Valproic acid use during radiation therapy for glioblastoma associated with improved survival. *Int J Radiat Oncol Biol Phys* 2013 in press.

5. Weller M, Gorlia T, Cairncross JG, van den Bent MJ, Mason WP, Belanger K, Brandes A, Bogdan U, Macdonald D, Forsyth PA, Rossetti AO, Lacombe D, Miriamanoff RO, Vecht CJ, Stupp R. Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. *Neurology* 2011;77:1156-1164.

6. De Wit-Kerkhof M, Dielemans J, Van Breemen MS, Zwinkels H, Walchenbach R, Taphoorn MJ, Vecht CJ. Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. *Neuro-Oncology* 2013;XX:XX-XX.

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